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(54) METHOD OF MANUFACTURING OBJECTS DESIGNED FOR REPEATED OR LONG TERM CONTACT WITH LIVE TISSUES

- (71) We, CESKOSLOVENSKA AKADEMIE
 VED, a Czechoslovakian Corporation of No.
 3 Narodni, Praha 1, Czechoslovakia, do
 hereby declare the invention, for which we
 pray that a patent may be granted to us,
 and the method by which it is to be per-
 formed, to be particularly described in
 and by the following statement:—
 The present invention relates to a method
 of manufacturing objects designed for re-
 peated or long-term contact with live tissues
 and mucous membranes, by polymerizing
 N-lower alkyl or N-lower hydroxyalkyl
 methacrylamides, if desired with a minor
 amount of one or more mono-olefinically
 unsaturated co-monomers, and with small
 amounts of a cross-linking monomer in the
 presence of water or a water-miscible liquid.
 As is well known, non-ionic hydrogels
 based on sparingly cross-linked polymers
 of glycol monomethacrylates or glycol
 monoacrylates have heretofore been used
 for manufacturing contact lenses, pros-
 theses for various somatic organs, implants,
 coatings of probes, catheters, drain tubes,
 cannulae, or the like, which materials are
 supposed to provide above all a good phy-
 siological compatibility and not to irritate
 living organisms. As it has been expected
 and also proved by laboratory tests on
 animals, analogous hydrogels comprising
 basic groups tend to irritate live tissues and
 are badly accepted by the host body, or in
 some cases healing of the tissues takes place
 tending to stick the article in position.
 According to the invention we provide a
 method of manufacturing articles designed
 for repeated or long term contact with live
 tissue and mucous membranes, comprising
 copolymerizing in a mould a monomer mix-
 ture containing more than 50 mol. percent
 of a hydrophilic monomer selected from
 an N-lower alkyl (as herein defined) meth-
 acrylamide and N-lower hydroxyalkyl (as
 herein defined) methacrylamide, and from
 0.1 to 2 mol. percent of a cross-linking com-
 pound having at least two polymerizable
 double bonds in its molecule, the copoly-
 merization being initiated by a free-radical
 polymerization catalyst or UV radiation and
 being carried out in the presence of water
 or a water-miscible liquid in a quantity
 such that the resulting copolymer takes on
 the shape of the mould, said cross-linking
 compound being soluble in the monomer
 mixture. Long-term laboratory tests car-
 ried out on a large number of rats have
 proved that tissue irritations, if any, are
 limited to several days after the implanta-
 tion of hydrogel whereupon they will dis-
 appear. Similarly as with other hydrogels
 and plastics in general, these materials get
 encapsulated by collagenous connective
 tissues but the encapsulating layer is suffi-
 ciently thin so as not to prevent both con-
 ventional surgical and prosthetic opera-
 tions.
 The monomer mixture may additionally
 include a mono-olefinically unsaturated
 monomer copolymerisable with said hydro-
 philic monomer. An advantage of both
 polymers and copolymers of N-alkyl meth-
 acrylamides resides in their considerable re-
 sistance to hydrolytic agents and en-
 zymes.
 As the mono-olefinically unsaturated
 monomer copolymerisable with the hydro-
 philic monomer, are suitable, for instance,
 methacrylonitrile, acrylonitrile, methacryl-
 amide, acrylamide, substituted acrylamides
 such as N-alkyl-acrylamides, and glycol
 mono-methacrylates derived from various
 glycols, such as ethylene glycol, di-ethylene
 glycol, tri-ethylene glycol, propylene glycol
 or butylene glycol. By appropriately choos-
 ing the composition of the monomer mix-
 ture it is possible to prepare a broad range
 of hydrophilic polymers, i.e. from sparingly
 cross-linked and highly swellable polymers
 of vitreous body types up to poorly water

swellable polymers. The hydrogels produced according to the present invention contain in equilibrium swollen state from 5 to 95 percent by weight of water calculated on the polymer weight.

The terms "lower alkyl" and "lower hydroxyalkyl", as used herein, mean, respectively, alkyl and hydroxyalkyl groups with 1 to 6 carbon atoms, with straight or branched chains. Water-miscible liquids that can be used are e.g. glycols, formamide and lower aliphatic alcohols.

The following examples are given as illustrative of the invention.

15 EXAMPLE I

An implant especially suitable as carrier for depositing an acidic medicament was prepared by polymerizing, in a suitable mould, a mixture of 79 percent of N-ethyl methacrylamide, one percent of diethylene glycol dimethacrylate, 0.02 percent of azobis-isobutyronitrile and water up to 100 percent. The mould was heated from the outside to 60° Centigrade. After 8 hours the polymerization was finished. The implant thoroughly washed was placed into a saline solution isotonic relative to the respective live tissue and comprising an appropriate medicament.

30 EXAMPLE II

A similar implant as described in Example I was prepared from a 70 percent aqueous solution of N-gamma-hydroxypropyl methacrylamide containing one percent of N,N-methylene-bis-methacrylamide and 0.05 percent of hydrogen peroxide. The polymerization was achieved within 8 hours heating the solution to 60° Centigrade in a mould.

40 EXAMPLE III

In a glass mould consisting of two ground plates spaced from each other by a distancing border layer, there was polymerized a 70 percent solution of N-hydroxy-n-butyl methacrylamide in n-butanol, comprising as cross-linking agent 0.3 percent of triethylene glycol dimethacrylate, and 0.02 percent of methyl azo-bis-isobutyrate. The polymerization was finished after 8 hours heating at 60° Centigrade. The thus formed foil washed in water and immersed in sterile physiological saline solution containing 350 p.p.m. of oxytetracycline hydrochloride was suitable as a temporary skin substitute after an accident.

EXAMPLE IV

In a glass mould as employed for manufacturing mammal prostheses there was heated a 70 percent aqueous solution of N-gamma-hydroxypropyl methacrylamide and N-propyl methacrylamide (2:1 ratio by

weight), containing 0.5 percent of N,N-methylene-bis-methacrylamide and 3 percent of methyl azo-bis-isobutyrate, for a period of 4 hours to 80° Centigrade, the mould having been filled initially to half of its capacity. The thus obtained spongy prosthesis was several times centrifuged, washed again in physiological saline solution and finally immersed into physiological saline solution containing 50 p.p.m. of tetracycline hydrochloride.

EXAMPLE V

Into a glass mould consisting of two ground plates spaced by a distancing layer at their partition an open-mesh polyester knitwork was inserted. The mould was then filled up at room temperature with an 80 percent aqueous solution of N-methyl methacrylamide and ethylene glycol monomethacrylate (4:1 ratio), containing 0.4 percent of ethylene glycol-bis-methacrylate and 0.05 percent of di-isopropyl percarbonate. The solution was freed of air bubbles by evacuation and tapping whereupon it was polymerized by heating to 60° Centigrade for 6 hours. The thus formed hydrogel sheet was suitable, for example, as a peritoneum substitute, or the like.

EXAMPLE VI

Into a glass tube there was inserted seamless polyester knitwork and poured an 80 percent solution of a mixture of N-gamma-hydroxypropyl methacrylamide with methacrylonitrile (5:1 ratio) in n-butanol, containing one percent of methylene-bis-acrylamide and 0.05 percent of di-isopropyl percarbonate. The tube was closed at both ends to serve as a mould and was set into rapid rotation about its longitudinal axis, its temperature having been maintained by means of an infra red radiator at 70° Centigrade. The polymerization finished, the tube was flushed with luke warm water till the butanol was removed whereupon the reinforced hydrogel polymerisate was withdrawn. The product was suitable, for instance, as an arterial prosthesis.

EXAMPLE VII

Elastic bodies designed to fill up post-operation cavities were manufactured by heating, in a mould, a 70 percent solution of a mixture of N-propyl methacrylamide with acrylamide (3:1 ratio), containing 0.5 percent of N,N-methylene-bis-methacrylamide and 0.05 percent of azo-bis-butyronitrile in n-butanol, for several hours at 70° Centigrade. After the polymerization had been achieved the bodies were removed from the mould, washed in warm distilled water and finally immersed into physiological saline solution having an admixture of streptomycin and p-aminosalicylic acid in

accordance with a physician's prescription.

All percentages referred to in the preceding Examples are to be understood by weight.

- 5 As hereinabove mentioned, the Examples are illustrative only and do not include all appropriate possibilities of mixed monomer compositions. The polymerisation can be promoted by means of various initiators which may be replaced by UV-irradiation, or if using special initiators capable of being decomposed into free radicals due to the absorption of rays within the visible spectrum band, the polymerization can be achieved by irradiation from a light source or by sun light. Likewise application or administration modes, i.e. types of objects designed for repeated or long-termed contact with live tissues or mucous membrane, are not limited to those disclosed in the above Examples. In this way it is also possible to prepare contraceptive intrauterine devices (CIUD), cosmetic prostheses, and the like.
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WHAT WE CLAIM IS:—

1. A method of manufacturing articles designed for repeated or long term contact with live tissue and mucous membranes, comprising copolymerizing in a mould a monomer mixture containing more than 50 mol. percent of a hydrophilic monomer selected from an N-lower alkyl (as herein
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defined) methacrylamide and N-lower hydroxyalkyl (as herein defined) methacrylamide, and from 0.1 to 2 mol. percent of a cross-linking compound having at least two polymerizable double bonds in its molecule, the copolymerization being initiated by a free-radical polymerization catalyst or UV radiation and being carried out in the presence of water or a water-miscible liquid in a quantity such that the resulting copolymer takes on the shape of the mould, said cross-linking compound being soluble in the monomer mixture.

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2. A method as claimed in claim 1, wherein the cross-linking compound having at least two polymerizable double bonds is N,N-methylene-bis-methacrylamide.

3. A method as claimed in claim 1 or claim 2, wherein the monomer mixture also contains a mono-olefinically unsaturated monomer copolymerizable with said hydrophilic monomer.

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4. A method of manufacturing articles as described in any one of the examples described herein.

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